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### REMARKS

Prior to this response, claims 1-3 were pending. By the present communication, claims 4-5 have been added, no claims have been cancelled and claims 1-3 have been amended. The new claim language adds no new matter, being fully supported by the Specification and original claims. Accordingly, claims 1-5 are currently pending.

#### **The Drawings**

The Office Action indicates that the drawings have been objected to under 37 CFR § 1.84 or § 1.152 and corrected drawings are required. To overcome the objection to the drawings, Applicant submits herewith as Exhibit A new formal drawings for Figures 1-8 of the application, which drawings are believed to meet all requirements under 37 CFR § 1.84 or § 1.152. Accordingly, reconsideration and withdrawal of the objection to the drawings are respectfully requested.

#### **The Rejection under 35 U.S.C. § 112, Second Paragraph**

Applicant respectfully traverses the rejection of claims 2 and 3 under 35 U.S.C. § 112, Second Paragraph, as allegedly being indefinite. With regard to claim 2, the Examiner asserts that the term "optionally" renders it unclear whether the limitation following the term is part of the claimed invention. To overcome the rejection, claim 2 has been amended to delete the term "optionally," thus overcoming the grounds for the rejection of claim 2.

With regard to claim 3, the Examiner asserts that the statement of the preamble is unclear because it allegedly is "unclear how a clone, which is an organism containing a specific DNA fragment, can display a protein characteristic" (Office Action, page 4). By the present

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communication, Applicant has amended the preamble to claim 3 to recite "A process of screening clones having DNA recovered from an uncultivated organism to identify a protein expressed therefrom having a specified enzymatic characteristic" thus avoiding any possible confusion concerning how the clone displays a protein characteristic.

In view of the above amendments, Applicants respectfully submit that claims 2-3 meet all requirements under 35 U.S.C. § 112, Second Paragraph.

**The Rejection under 35 U.S.C. § 112, First Paragraph – Written Description**

Applicant respectfully traverses the rejection of claims 1-3 under 35 U.S.C. § 112, First Paragraph, for containing subject matter that allegedly is not adequately described in the Specification so that those of skill in the art would understand that Applicant had possession of the claimed invention. By the present communication, claims 1-3 have been amended to recite that the desired characteristic is an enzyme characteristic. Applicant disagrees with the Examiner's assertion that the Specification shows that the Applicant had described the invention in such a way that those of skill in the art would come to the conclusion that Applicant "had possession of the invention" only with respect to identifying *E. coli* clones comprising DNA isolated from a picoplankton sample wherein the clones express enzymes having hydrolase activity which are active after heating to 70° C for 45 minutes (Office Action, pages 4-5).

Applicant respectfully submits that those of skill in the art would understand that Applicant's description of DNA isolated from a picoplankton sample that was expressed in *E. coli* and the expression products screened for hydrolase activity after heating to 70° C for 45 minutes was merely an illustration the invention, not the sole embodiment of the invention. For example, the Examiner acknowledges that the Specification "discloses that the method can be

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used to detect pH stability, temperature stability and substrate specificity” of enzymes (Office Action, page 5). It is well settled law, that an Applicant’s claims are not to be limited to the scope of the examples, and Applicants respectfully submit that to limit the claims for alleged lack of description as asserted by the Examiner is to limit the invention to the examples used to illustrate the invention.

Moreover, the description of the invention in the Specification is considered to be supplemented by the knowledge of the art. At the filing of the present application, the skill of the art with respect to liquid phase assays for determining whether a substrate is acted upon by an enzyme was well developed. Assays for enzyme activity are known for many enzyme activities, and Applicant respectfully submits that the particular known enzyme activity assay used in the final step of the invention methods is not beyond the routine skill of the art. Such assays can be conducted under a variety of test conditions to determine such characteristics as pH stability, temperature stability and substrate specificity of the test enzyme.

In addition, with regard to the Examiner’s conclusory assertion that those of skill in the art would not know how to discount the alleged “false positives” that might result from enzymes expressed by the host expression cell used, Applicants submit that the Examiner has provided no reasons in support of this conclusory assertion as is required. The Examiner’s assertion that heating the cell sample to 70° C to inactivate enzymes endogenous to the host cell would in many cases inactivate the molecule being tested seems to ignore the fact that if the recombinant enzyme is inactivated, that would not provide the information the method is meant to provide in the example at issue.

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In assays not intended to identify recombinant enzymes that remain functional at 70° C, the technique of subtracting host cell molecules from recombinant molecules was well known in the art at the filing of the present application. For example, the complete genome of *E. coli* is known. In the invention methods as defined by amended claim 3, the step of recovering DNA selectively by recovering those DNAs that hybridize to “probes containing a full-length coding region sequence or a partial coding region sequence for an enzyme having the specified enzymatic characteristic” would considerably reduce the number of molecules that would need to be “subtracted.”

In view of the amendments and above arguments, Applicant respectfully submits that those of skill in the art would reasonably conclude that Applicant had possession of the claimed invention at the filing of the application, and reconsideration and withdrawal of the rejection are respectfully requested.

**The Rejection under 35 U.S.C. § 112, First Paragraph -- Enablement**

Applicant respectfully traverses the rejection of claims 1-3 under 35 U.S.C. § 112, First Paragraph, for allegedly lacking enablement. Applicant disagrees with the Examiner's assertion that the Specification provides an enabling disclosure only for the example wherein *E. coli* clones of a recombinant DNA library derived from an uncultivated microorganism are screened for hydrolase activity after heating to 70° C. Applicant respectfully submits that the comments above regarding the high level of skill in the art and how the knowledge of the art is deemed to supplement the specification apply equally and are incorporated here. As claims 1-3 have been amended to recite that the molecules screened are enzymes and the type of characteristic tested is an enzymatic characteristic, the Examiner's assertion that “the scope of the claim[s] is not

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commensurate with the enablement provided in regard to the infinite number of proteins and protein's characteristics encompassed by the claims" (Office Action, page 6) is no longer apposite. Accordingly, Applicant respectfully submits that given the guidelines in the Specification and the knowledge in the art, those of skill in the art could practice the claimed invention methods without undue experimentation. Accordingly, reconsideration and withdrawal of the rejection of claims 1-3 under 35 U.S.C. § 112, First Paragraph for allegedly lacking an enabling disclosure are respectfully requested.

**The Rejection under 35 U.S.C. § 103**

Applicant respectfully traverses the rejection of claims 1-3 under 35 U.S.C. § 103 as allegedly being unpatentable over Yen et al. (U.S. Patent No. 5,171,684; hereinafter "Yen") in view of More et al. (Appl. Environ. Microbiol. 60(5):1572-1580, 1994; hereinafter "More"). The invention processes for identifying clones of a recombinant library produced from DNA derived from at least one uncultivated organism which express an enzyme with a desired characteristic, as defined by amended claim 1, distinguish over the combined disclosures of Yen and More at least by requiring "screening in the liquid phase a library of expression clones randomly produced from DNA of at least one uncultivated organism, said screening being effected on expression products of said clones to thereby identify clones which express an enzyme with a desired characteristic.

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The invention processes of screening clones having DNA recovered from an uncultivated organism to identify a protein, as defined by amended claim 3, distinguish over the combined disclosures of Yen and More by requiring:

screening for a specified enzyme characteristic in a library of clones prepared by  
(i) recovering DNA selectively from a DNA population derived from at least one uncultivated organism by contacting the recovered DNA in liquid phase assay under hybridizing conditions with at least one hybridizing probe containing a full-length coding region sequence or a partial coding region sequence for an enzyme having the specified enzymatic characteristic; (ii) transforming a host cell with the recovered DNA to produce a library of clones; and (iii) expressing the library of clones to obtain expression products which are screened for the specified enzymatic characteristic.

Applicant respectfully submits that Yen fails to suggest the invention processes because in Yen's method the isolated DNA was pretreated so as to bias the DNA towards a particular known enzyme with a restriction endonuclease whose active site was known to exist in some or all of the genes encoding the predetermined target protein (enzyme). In addition, the Pm KR-1 cells of Yen et al., although mutagenized, were all obtained from the same species of organism and thus are not "randomly produced" as is required in the invention process of claim 1. In addition, Yen fails to suggest screening a library from a mixed population of uncultured organisms to determine those having a desired enzymatic property, as is required in the process of claim 3. Yen knows in advance that all of the molecules in the library to be screened are but mutants of a single known DNA.

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More fails to cure the deficiencies in the disclosure of Yen for suggesting the invention methods. Although More describes methods for isolation of DNA from a sediment sample containing a mixed population of organisms, More amplifies a single predetermined gene, *nahR*, encoding the regulatory gene for naphthalene catabolism in *Pseudomonas putida* G7 and only for the purpose of determining the performance efficiency of the DNA extraction procedures being tested. Thus, like Yen, More fails to suggest how a library from a mixed population of uncultured organisms would be prepared for screening to identify unknown DNAs encoding proteins having a desired enzymatic property.

In addition, due to these considerable differences between the combined disclosures of Yen and More, Applicant respectfully submits that the references themselves provide no suggestions for their combination to arrive at the present invention since neither disclosure pertains to screening a DNA library containing DNA obtained from a mixed population of organisms or uncultured organisms.

Moreover, Applicant respectfully submits that even if those of skill in the art were motivated to combine the references, as suggested by the Examiner, there could be no reasonable expectation of success because neither reference discloses how to prepare a DNA library containing DNA obtained from at least one uncultured (i.e., unknown) organism or from a mixed population of such organisms for screening to identify clones with DNA encoding an enzyme having a desired enzymatic characteristic.

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Accordingly, Applicants submit that prima facie obviousness of claims 1-3 is not established over the combined disclosures of Yen and More and reconsideration and withdrawal of the rejection are respectfully requested.

**The Double Patenting Rejection**

Applicant respectfully traverses the provisional rejection of claims 1-3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U. S. Patent No. 6,280,926 in view of More.

Applicant respectfully traverses the provisional rejection of claims 1-3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U. S. Patent No. 6,168,919 in view of More.

Applicant respectfully traverses the provisional rejection of claims 1-3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 5,958,672 in view of More.

Applicant respectfully traverses the provisional rejection of claims 1-3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 32-47 of copending application Serial No. 09/421,629 in view of More.

Applicant respectfully traverses the provisional rejection of claims 1-3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 14, and 16 of copending application Serial No. 09/467,740 in view of More.

Applicant respectfully traverses the provisional rejection of claims 1-3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20, 23-25, and 27-28 of copending application Serial No. 09/713,176 in view of More.

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Applicant respectfully traverses the provisional rejection of claims 1-3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending application Serial No. 09/861,267 in view of More.

Applicant respectfully traverses the provisional rejection of claims 1-3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of copending application No. Serial 09/875,412 in view of More.

In traversal of the above provisional rejections for alleged double patenting, Applicants submit herewith a Terminal disclaimer disclaiming the terminal part of any patent that may issue on claims of the present application that would extend beyond expiration of any of the above issued patents and patents that may issue from the above co-pending patent applications. In addition, Applicant submits that the present application and all of the co-pending applications and issued patents referenced in the Terminal Disclaimer were co-owned by Diversa Corporation at the filing date of the present application. In view of the Terminal Disclaimer submitted herewith, Applicant respectfully submits that all of the patent applications and issued patents referenced in the terminal disclaimer are not available as prior art against the present application.

In addition, Applicant respectfully submits that the teachings of More alone are not sufficient to render unpatentable the subject matter of the invention methods, as defined by present claims 1-5. Although More describes methods for isolation of DNA from a sediment sample containing a mixed population of organisms, More amplifies a single predetermined gene, *nahR*, encoding the regulatory gene for naphthalene catabolism in *Pseudomonas putida* G7 and only for the purpose of determining the performance efficiency of the DNA extraction procedures tested by More. More does not prepare a library for screening or screen such a library

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for any type of molecule or activity. Thus, More fails to suggest how a library from an uncultured organism or a mixed population of uncultured organisms would be prepared for screening to identify unknown DNAs encoding proteins having a desired enzymatic property. In light of the Terminal Disclaimer and above remarks concerning More's deficiency for disclosing the present invention, Applicants respectfully request reconsideration and withdrawal of the double patenting rejection for alleged obviousness-type double patenting.

In view of the Terminal Disclaimer and above amendments and remarks, Applicant respectfully submits that all claims are now in condition for allowance, which is respectfully requested. If the Examiner would like to discuss any issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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